UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,905	03/23/2004	David Scheinberg	D6499	2406

7590 04/06/2006

EXAMINER
FETTEROLF, BRANDON J

ART UNIT	PAPER NUMBER
1642	

Benjamin Aaron Adler
ADLER & ASSOCIATES
8011 Candle Lane
Houston, TX 77071

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,905	SCHEINBERG ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-61 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-5,7-17,19-25,27-36,38-43,45-52 and 55-61 is/are rejected.

7)☒ Claim(s) 6,18,26,37,44,53 and 54 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 23 March 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Scheinberg et al.

DETAILED ACTION

Application Status

Claims 1-61 are currently pending and under consideration.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: an administration step describing what is being administered in order to obtain the preamble of the method objectives.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7-14, 16-17, 19-25, 27-33, 35-36, 38-43, 45-51 and 55-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of adjuvants further defined by three subgenus's which prevent the accumulation of a metal in a kidney. Thus, the claims encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property. However, the written description only sets forth three subgenus consisting of: (1) chelators such as dithiol chelators and ethylenediamine/diethylenetriamine tetra-acetic acid chelators; (2) the diuretics such as furosemide, chlorthiazide, hydrochlorothiazide, bumex, or other loop diuretics; and (3) competitive metal blockers such as bismuth subnitrate or bismuth subcitrate.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The specification teaches (page 19, lines 14-15) that specific adjuvants of the invention include, chelators, diuretics or competitive metal blockers. With regard to the chelators, the specification teaches (page 18, line 20 to page 19, line 5) that chelators include, but are not limited to dithiol chelators such as 2,3 dimercapto-1-propane sulfonic acid (DMPS) and meso 2,3-dimercapto succinic acid (DMSA) or other chelators such as ethylenediamine tetra-acetic acid (EDTA), diethylenetriamine petaacetic acid (DTPA), calcium diethylenetriamine pentaacetic acid (Ca-DTPA), or zinc diethylenetriamine pentaacetic acid (ZN-DTPA). With regards to the diuretics, the specification teaches (page 19, lines 9-10) that diuretics include, but are not limited to furosemide, chlorthiazide, hydrochlorothiazide, bumex, or other loop diuretics. With regards to the metal

blocker, the specification teaches (page 19, lines 11-13) that metal blockers include nonradioactive bismuth competitor's such as bismuth subnitrate or bismuth subcitrate. Thus, while the specification reasonably conveys a number of species for each sub genus, there is insufficient written description encompassing any "adjuvant and/or chelate, diuretic or competitive metal blocker effective for preventing accumulation of a metal in a kidney" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "adjuvant and/or chelate, diuretic or competitive metal blocker" are not set forth in the specification as-filed, commensurate in scope with the claimed invention. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of compounds that encompass the genus of adjuvants further defined by three subgenus's which prevent the accumulation of a metal in a kidney nor does it provide a description of structural features that are common to the genus. Since the disclosure

fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of genus of adjuvants further defined by three subgenus's which prevent the accumulation of a metal in a kidney, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 7-8, 10-11, 13-15, 19, 32-34, 49-52, 55 and 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennel et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244) in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113).

Kennel et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate (abstract). However, the reference teaches that while the isotope coupled to the targeting monoclonal antibody delivers a tumorcidal dose to the lung, the radiotoxicity associated with decay daughter isotopes released from the target organ limit the effectiveness of the therapy (page 242, 2nd column, last paragraph). For example, Kennel et al. teach immediately after organ harvest, the level of ^{213}Bi, the third decay daughter of ^{225}Ac, was found to be deficient in the lungs and to be in excess in the kidneys (page 239, 1st column paragraph to 2nd column).

Kennel et al. do not explicitly teach administering an adjuvant such as a dithiol chelate in combination with the ^{225}Ac conjugate for reducing the nephrotoxicity of ^{225}Ac.

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made to administer an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac isotope bound to a HEHA-Mab 201B conjugate as taught by Kennel et al in view of Jones et al. teachings that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. One would have been motivated to do so because as taught by Jones et al., administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac isotope bound to a HEHA-Mab 201B conjugate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Claims 5 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennel et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244) and Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113) in further view of Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60).

Kennel et al. teach, as applied to claims 1-4, 7-8, 10-11, 13-15, 19, 32-34, 49-52, 55 and 58-60 above, a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate (abstract). However, the reference teaches that while the isotope coupled to the targeting monoclonal antibody delivers a tumorcidal dose to the lung, the radiotoxicity associated with decay daughter isotopes released from the target organ limit the effectiveness of the therapy (page 242, 2nd column, last paragraph). For example, Kennel et al. teach immediately after organ harvest, the level of ^{213}Bi, the third decay daughter of ^{225}Ac, was found to be deficient in the lungs and to be in excess in the kidneys (page 239, 1st column paragraph to 2nd column).

Keller et al. do not explicitly teach the administration of a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention

was made to administer a diuretic such as furosemide in combination with an ^{225}Ac conjugate as taught by Keller et al. in view of the teachings of Schilcher et al. that furosemide prevents the occurrence of cumulative nephrotoxiticy. One would have been motivated to do so because Shlicher et al. teach that the furosemide is clinically used to prevent the cumulative nephrotoxicity associated with metal treatment of tumors. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a diuretic such as furosemide in combination with an ^{225}Ac conjugate comprising a functionalized chelate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Claims 1-4, 7-15, 19-23, 32-34, 49-52, 55 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheinberg et al. (US 2002/0058007, 2002) in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113).

Scheinberg et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 2, paragraph 0016). With regards to the cancer, the publication teaches (page 4, paragraph 0037) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the publication teaches (page 2, paragraph 0017) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 2, paragraph 0021) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the daughters from nontargeted constructs (beginning on page 8, 2nd column, Example 9).

Scheinberg et al. does not explicitly teach administering an adjuvant such as a dithiol chelate in combination with the ^{225}Ac conjugate for reducing the nephrotoxicity of ^{225}Ac.

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature

release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate comprising a functionalized chelate as taught by Shreinberg et al. in view of Jones et al. teachings that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. One would have been motivated to do so because as taught by Jones et al., administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate comprising a functionalized chelate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Claims 5 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheinberg et al. (US 2002/0058007, 2002) and Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113) in further view of Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60).

The combination of Scheinberg et al. and Jones et al. teach, as applied to claims 1-4, 7-15, 19-23, 32-34, 49-52, 55 and 58-61, a method of treating cancerous cells with alpha particles

comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate consisting of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac and an effective dose of a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS). Specifically, Jones et al. teaches that administration of 2,3-dimercapto-1-propanesulfonic acid (DMPS) accelerates the clearance and reduces the early and late accumulation of late bismuth particles in the kidney which is a target for dose limiting toxicity (page 112, 1st column, 1st full paragraph and page 112, 2nd column, *Conclusion*).

The combination of Scheinberg et al. and Jones et al. do not explicitly teach the administration of a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer a diuretic such as furosemide in combination with an ^{225}Ac conjugate as taught by Scheinberg et al. in view of the teachings of Schilcher et al. that furosemide prevents the occurrence of cumulative nephrotoxitiey. One would have been motivated to do so because Jones et al. teaches that that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a diuretic such as furosemide in combination with an ^{225}Ac conjugate comprising a functionalized chelate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Claims 1-4, 7-15, 19-23, 32-34, 49-52, 55 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113).

McDevitt et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 1537, Abstract). With regards to the cancer, the reference teaches (page 1537, Abstract)

that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the reference teaches (page 1538, 1st column, 2nd full paragraph) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 1538, 1st column, 2nd full paragraph) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the daughters from nontargeted constructs (page 1538, Figure 1B).

McDevitt et al. does not explicitly teach the administering of an adjuvant such as a dithiol chelate in combination with the ^{225}Ac conjugate for reducing the nephrotoxicity of ^{225}Ac.

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and the mice were then maintained on the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in

combination with an ^{225}Ac conjugate comprising a functionalized chelate as taught by McDevitt et al. in view of Jones et al. teachings that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. One would have been motivated to do so because Jones et al. teaches that the administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate comprising a functionalized chelate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Claims 5 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDevitt et al. (Science 2001; 294: 1537-1540) and Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113) in further view of Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60).

The combination of McDevitt et al. and Jones et al. teach, as applied to claims 1-4, 7-15, 19-23, 32-34, 49-52, 55 and 58-61 above, a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate consisting of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac and an effective dose of a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS). Specifically, Jones et al. teaches that administration of 2,3-dimercapto-1-propanesulfonic acid (DMPS) accelerates the clearance and reduces the early and late accumulation of late bismuth particles in the kidney which is a target for dose limiting toxicity (page 112, 1st column, 1st full paragraph and page 112, 2nd column, *Conclusion*).

The combination of McDevitt et al. and Jones et al. do not explicitly teach the administration of a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer a diuretic such as furosemide in combination with an ^{225}Ac conjugate as taught by McDevitt et al. in view of the teachings of Schilcher et al. that furosemide prevents the

occurrence of cumulative nephrotoxiticy. One would have been motivated to do so because Jones et al. teaches that that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a diuretic such as furosemide in combination with an ^{225}Ac conjugate comprising a functionalized chelate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Note: Claims 4, 18, 26, 37, 44 and 53-54 are objected to as being dependent from a rejected independent claim.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

BF